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10/809,845	03/26/2004	Sangita	033166-024	8163

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EXAMINER	
CHUNG, SUSANNAH LEE	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/809,845	SANGITA ET AL.	
	Examiner	Art Unit	
	Susannah Chung	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *4,6-37 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 38-40, 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-47 are pending in the instant application.

Priority

This application claims benefit of 60/458,401, filed 03/31/2003.

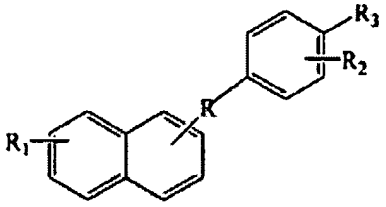
Response to Election/Restrictions

Applicant's election *without traverse* of Group I, claims 1-5 and 38-47, in the reply filed on 26 July 2006 is acknowledged. Specially, the election of species of (4-methylthiophenyl)-naphth-1-yl-carbinol.

Scope of the Elected Invention

Claims 1-47 are pending in this application.

The scope of the elected subject matter that will be examined and searched is as follows:

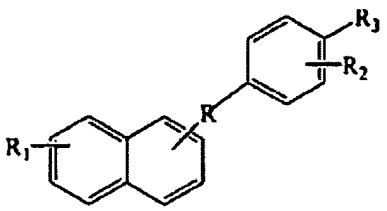
Compounds of formula (I), 

, depicted in claim 1, page 43, wherein:

R is CHOH; **R1** is H, C1-6 alkyl; **R2** is H, C1-6 alkyl; and **R3** is substituted mercapto.

Scope of Withdrawn Subject Matter

Claims 4, 6-37, and 41 are withdrawn from further consideration by the examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

Compounds of formula (I),  , depicted in claim 1, page 43,

wherein: **R** is anything other than CHOH.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

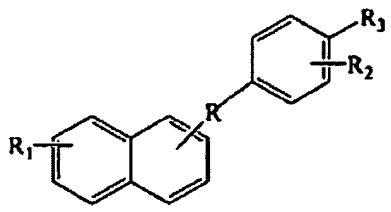
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

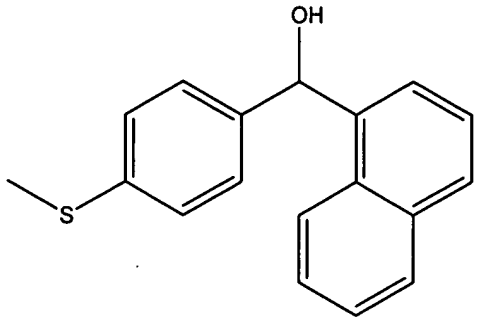
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5, 38-40, and 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rotstein et al., U.S. Pat. No. 5,962,531 (1999).

Applicants instant elected invention teaches the compound of formula,

 , depicted in claim 1, wherein: **R** is CHOH; **R1** is H, C1-6 alkyl;

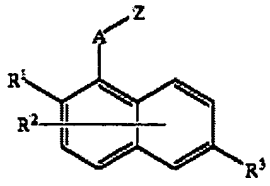
R2 is H, C1-6 alkyl; and **R3** is S-CH3, yielding the elected compound, (4-methylthiophenyl)-



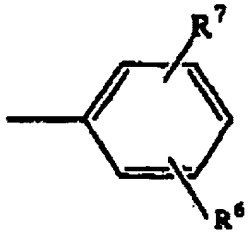
naphth-1-yl-carbinol, .

Determination of the scope and content of the prior art (MPEP § 2141.01)

Rotstein teaches 5-aroylnaphthalene derivatives as anti-inflammatory agents of formula,



, wherein **A** is CHOH; **Z** is the compound of formula (B),



, wherein

R^6 and R^7 are independently selected from hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, acyl, alkylthio, cycloalkylthio, cycloalkylalkylthio, alkoxy, cycloalkyloxy,cycloalkylalkyloxy, haloalkyloxy, alkenyl, halo, cyano, nitro, hydroxy, or —NR^9R^{10} where R^9 and R^{10} are independently hydrogen, alkyl, or acyl; or R^6 and R^7 when they are adjacent to each other form methylenedioxy or ethylenedioxy; R^8 is hydrogen, alkyl, haloalkyl, alkoxy, cycloalkyloxy, haloalkyloxy, alkylthio, cycloalkylthio, nitro, cyano, hydroxy, or halo;

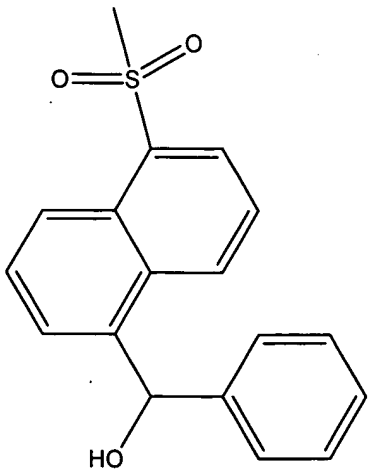
R3 is SO2R12 or SO2NR13R14,

R^1 is hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, alkenyloxy, cycloalkyloxy, cycloalkylalkyloxy, haloalkyloxy, hydroxyalkyloxy, alkoxyalkyloxy, alkylthio, cycloalkylthio, cycloalkylalkylthio, hydroxy, halo, cyano, carboxy, alkoxycarbonyl, acyl, —C=NOR^4, —NR^{9}R^{10}, —CONR^{9}R^{10}, —OCONR^{9}R^{10}, or —OSO$_2$R^{11} where R^4, R^9, and R^{10} are as previously defined and R^{11} is alkyl, cycloalkyl, or haloalkyl; useful in the treatment of cancer. (See U.S. Pat. No. 5,962,531, Column 22, lines 38-40 and Column 34, lines 23-68).

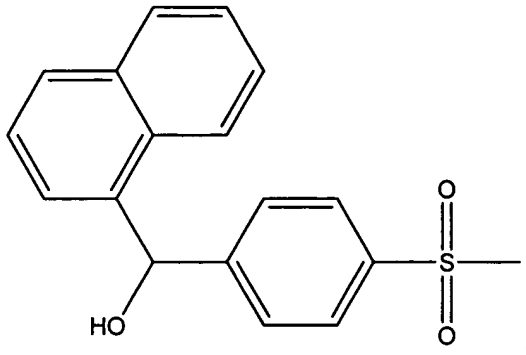
Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Rotstein and the instant claims is that they are isomers of each other. The sulfonyl or substituted mercapto functional group is in different positions on the core structure. In the prior art of Rotstein the functional group is attached to the naphthalene group, while in the instant application it is attached to the phenyl group.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Rotstein to make products useful in the treatment of cancer, wherein (1-(methylsulfonyl)naphthalen-5-yl)(phenyl)methanol, 

, is (4-methylsulfonylphenyl)-naphth-1-yl-

carbinol,  , CAS RN 774235-16-4, by changing the position of the methylsulfonyl functional group from the naphthyl ring to the phenyl ring. It should be noted, that adjacent homologues and structural isomers are generally so structurally similar that "without more" such structural similarity could give rise to prima facie obviousness. In re Wilder, 563 F.2d 457, 195 USPQ 426.

Guided by the teachings of Rotstein one skilled in the art would be able to make similar compounds by changing the positions of the various functional groups taught in Rotstein. The motivation would be to prepare similar compounds that are pharmacologically active compounds useful in the treatment of cancer and other disorders.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specificall y, Claim 1 is indefinite because the substituent "R" is defined twice. The first definition of R is in claim 1, line 4,

wherein R is selected from the group consisting of CO, CH_2 and $CHOR_4$,

The second definition of R is in claim 1, line 10, wherein

R is CO or CHOH, C_3-C_7 cycloalkyl, C_3-C_7 heterocyclic alkyl in which the heterocycle ring is selected from the group consisting of pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrol, 2H-pyrrol, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholino, thiomorpholino, isothiazolyl, isozazolyl, oxazolyl, oxadiazolyl, thiadiazolyl and thiazolyl, optionally substituted with 1 to 3 substituents, independently selected from the group consisting of H, OH, halo, nitro, cyano, SH and SO_2R_7

It is unclear which definition of R is intended.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-40 and 42-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the specification **while being enabled for *treating* estrogen deficiency, osteoporosis, bone loss, bone formation and breast cancer** (see specification, p. 32-42, [0110-0143], Biological Evaluation) does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 38-40 and 42-47 of the present invention below:

(1) The Nature of the Invention

Claims 38-40 and 42-47 are directed to

38. **A pharmaceutical composition for treatment and/or prevention of disease syndromes related to estrogen deficiency, osteoporosis, bone loss, bone formation, cardiovascular disorders, neurodegenerative disorders, menopausal disorders, physiological disorders, diabetes disorders, prostatic carcinoma, cancer of breast, cancer of uterus, cancer of the cervix and cancer of the colon, threatened or habitual abortion, obesity, ovarian development or function, post-partum lactation and depression in mammals including humans, comprising a thus effective amount of a mercaptophenyl naphthyl methane compound having structural formula 1**

(2) The Breadth of the claims

Claims 38-40 and 42-47 will be given its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

In view of this rule, all of the disorders in Claims 38-40 and 42-47 will be interpreted broadly to encompass all types of diseases, which is related to disorder claimed. The generic disorders of cardiovascular disorders, neurodegenerative disorders, menopausal disorders; physiological disorders, diabetes disorders, etc..., will be interpreted to encompass all diseases that could fall under the generic disorder. For example, cardiovascular disorders will be interpreted to encompass diseases such as hyperlipidaemia and atherosclerosis, while neurodegenerative disorders will be interpreted to encompass diseases such as Alzheimer's disease and Parkinson's disease.

(3) The state of the prior art

Estrogen deficiency

It was known in the art at the time of this application that the compound of the instant application can treat estrogen deficiency. (See specification, pages 39-42, [0132-0142]) Test procedure and data is provided for the evaluation of estrogen agonistic activity. The data shows that the relative binding affinity of the compounds for the estrogen receptor is high.

Osteoporosis, Bone loss, and Bone formation

It was known in the art at the time of this application that the compound of the instant application can treat osteporosis, bone loss and bone formation. (See specification, pages 33-35, [0112-0118]) Test procedure and data is provided for the evaluation of antiosteoporosis

(antireoptive) activity in vitro. The data shows that the compounds of the instant application are useful as antiresorptive agents in the treatment of osteoporosis, bone loss and bone formation.

Breast cancer

It was known in the art at the time of this application that the compound of the instant application can treat estrogen deficiency. (See specification, pages 36-38, [0123-0138]) Test procedure and data is provided for the evaluation of antiproliferative/cytotoxic activity in vivo. The compounds of the instant application were tested in vivo for anticancer breast activity using the rodent model of hormone responsive breast cancer, namely 7,12-dimethylbenz(a)anthracene (DMBA) induced rat mammary tumor model. The compound is active against mammary tumor as demonstrated by a decrease of the tumor volume.

Preventing diseases

The state of the art at the time of this application was that no single class of compound is known to *prevent* the diseases claimed. Applicant's specification does not provide support for preventing the diseases. Applicant can overcome this rejection by deleting the term "prevention" in claim 38.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific

enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether in vitro activity against estrogen deficiency, osteoporosis, bone loss, bone formation, and breast cancer by one of the compounds of the present invention could be reliably and predictably extrapolated to in vivo activity in patients with cardiovascular disorders, neurodegenerative disorders or any of the other complex and diverse diseases claimed. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the instant compounds play an important role in *treating* estrogen deficiency, osteoporosis, bone loss, bone formation, and breast cancer only. There is insufficient guidance in the specification for the role the instant compounds play in the treatment of cardiovascular disorders, neurodegenerative disorders, menopausal disorders, etc....

(7) The presence or absence of working examples

As noted in the previous section, the specification discloses working examples for the treatment of estrogen deficiency, osteoporosis, bone loss, bone formation, and breast cancer. However, the specification has no working examples, such as in vivo or in vitro studies of the role the instant compounds play in the treatment of the other disorders claimed.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instant compounds in the treatment of all the disorders claimed, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the many claimed compounds within the scope of the invention with a reasonable expectation of success.

As stated earlier, the guidance provided in the specification about the use of the instant compounds in the treatment of estrogen deficiency, osteoporosis, bone loss, bone formation, and breast cancer, along with the prior art is sufficient to enable one skilled in the art to practice this invention without an undue amount of experimentation.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Date: 16 August 2006